Balkan Nephropathy

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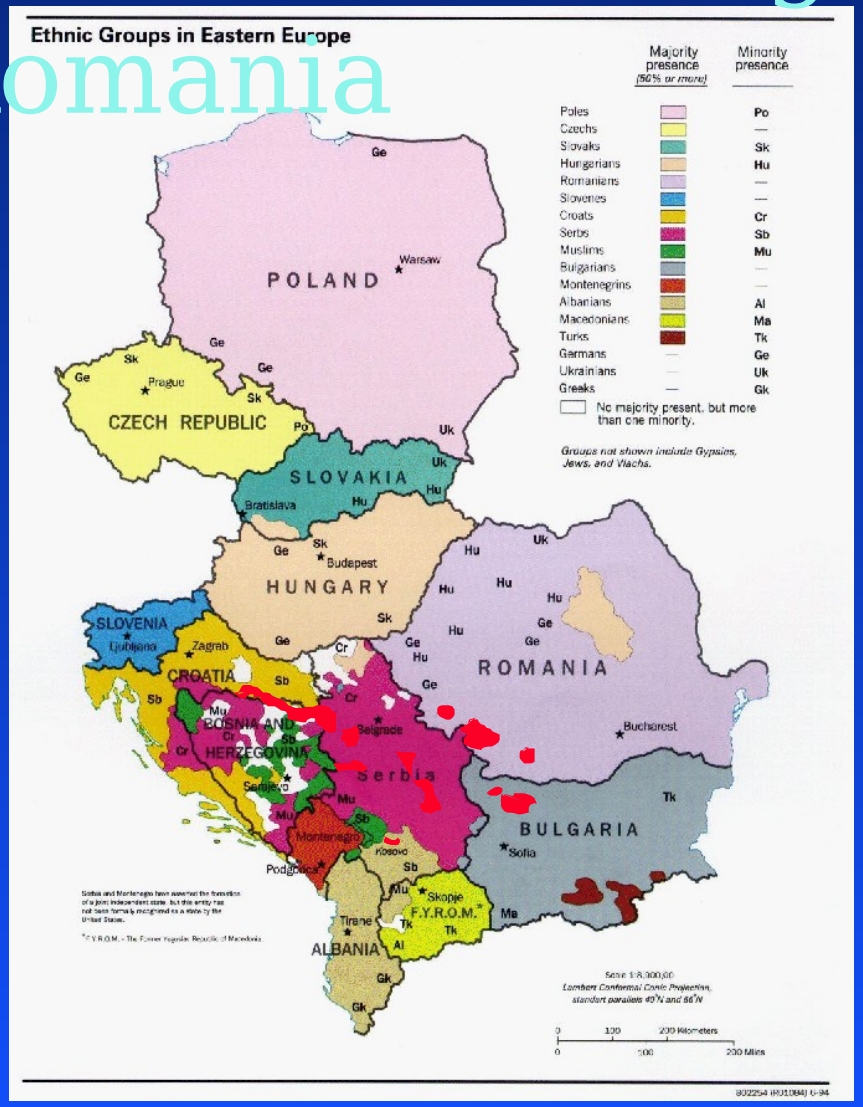
Balkan Endemic Nephropathy

- Chronic Tubulointerstitial Disease
- Affecting thousands of people
- Progresses to renal failure, usually in the 4th to 5th decade.
- Found in small agricultural villages
- Mosaic like distribution has not changed since initial descriptions in 1950's

BEN is found in Serbia, Croatia, Bosnia, Bulgaria and Romania



Endemic Desease

Clusters occur in the alluvian plains along affluents of the Danube

R. Sava

R. Danube

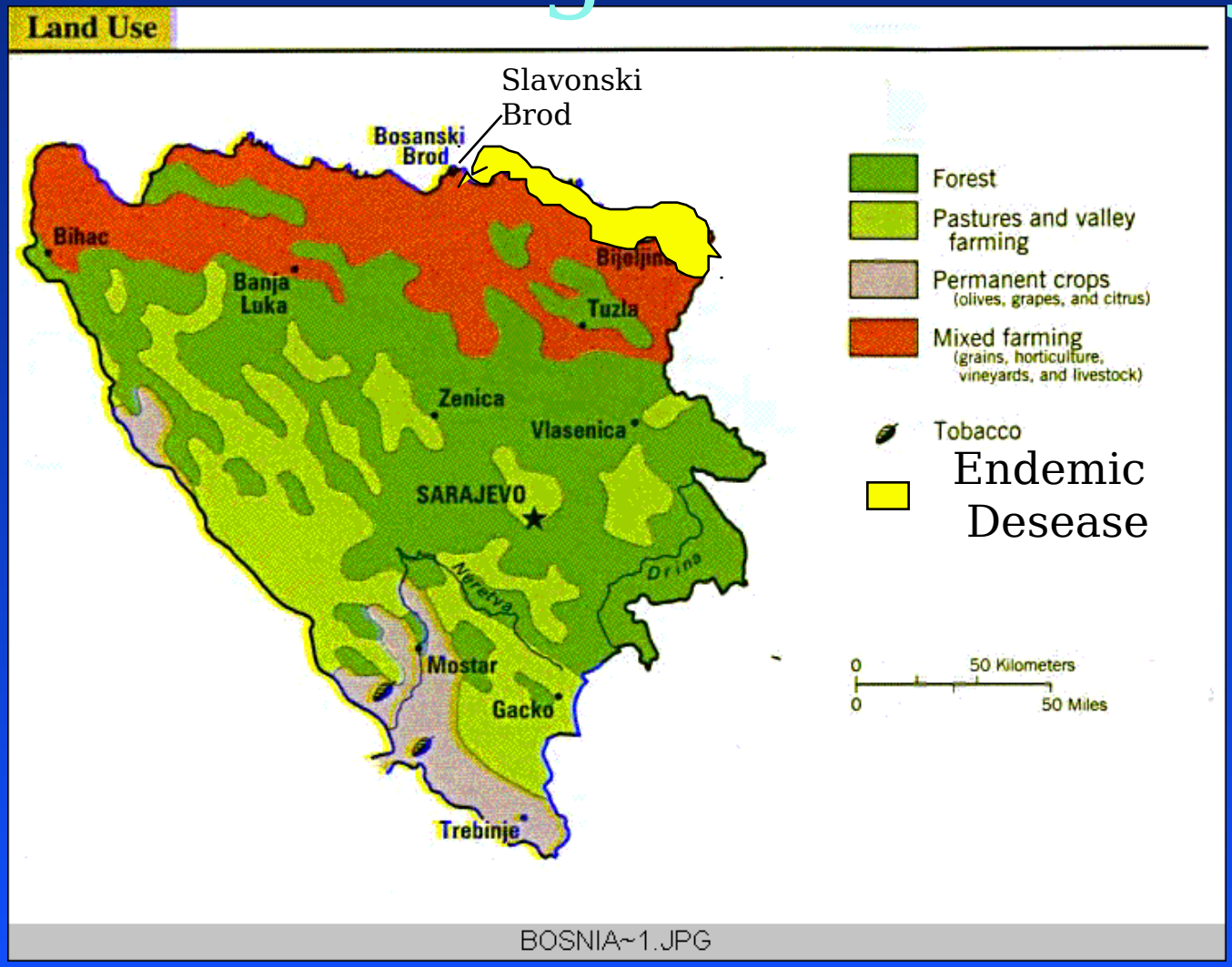
R. Morava

Endemic Desease

One endemic region touches area currently protected by U.S.A.

Endemic
Desease

Endemic region is involved in grain farming



‘endemic Vratza nephritis’

- 1940’s local physicians noted that kidney disease was common in certain settlements
- 1950-54 Tanchex studied 664 patients
- Clusters of patients found in villages, families and even houses in Vratza region
- 1957 ‘ family outbreak’ in Serbia killing mother & 2 adolescent daughters, causing severe kidney damage in father & son in 3 months, leading to name BEN.

Epidemiology of BEN

- Prevalence of nephritis in endangered population ranges from 2 - 10%
- b-2 microglobulinuria in 20-25 %
- BEN occurs in emigrants and immigrants after long exposure to endemic region
- High incidence of urothelial tumors (slowly progressive) 100 times the expected rate
  - (2-47 % of patients with BEN)

Comparisons of Croatian aborigines & Ukarainian immigrants in Slavonski Brod

	Croatians		Ukrainians	
	endemic	non-endemic	endemic	no
SSA	15.6 %	4.7	11.9	
LMW	11.0	3.6	10.2	
Creat	30.4	3.2	43.7	

Ceovic, Hrabar & Radonic
Nephron, 1985

Prevalence of BEN in area around Slavonski Brod

	No. of inhab.	1957	1977	1987	88	89
Banovici	372	-	2.0	2.2	-	1.0
Kaniza	755	-	4.1	2.5	1.0	1
Slavanski Kobas	1461	2.3	2.4	-	0.8	
Sumece	552	-	1.7	0.6	-	

Clinical Features of BEN

- Salt Wasting
  - Normotensive
  - without edema
- Anemia
- Tubular Proteinuria
- Scarce urinary sediment
- pallor & xanthochromia of palms & soles
- Hematuria suggests urothelial tumor

Tubular proteinuria in BEN

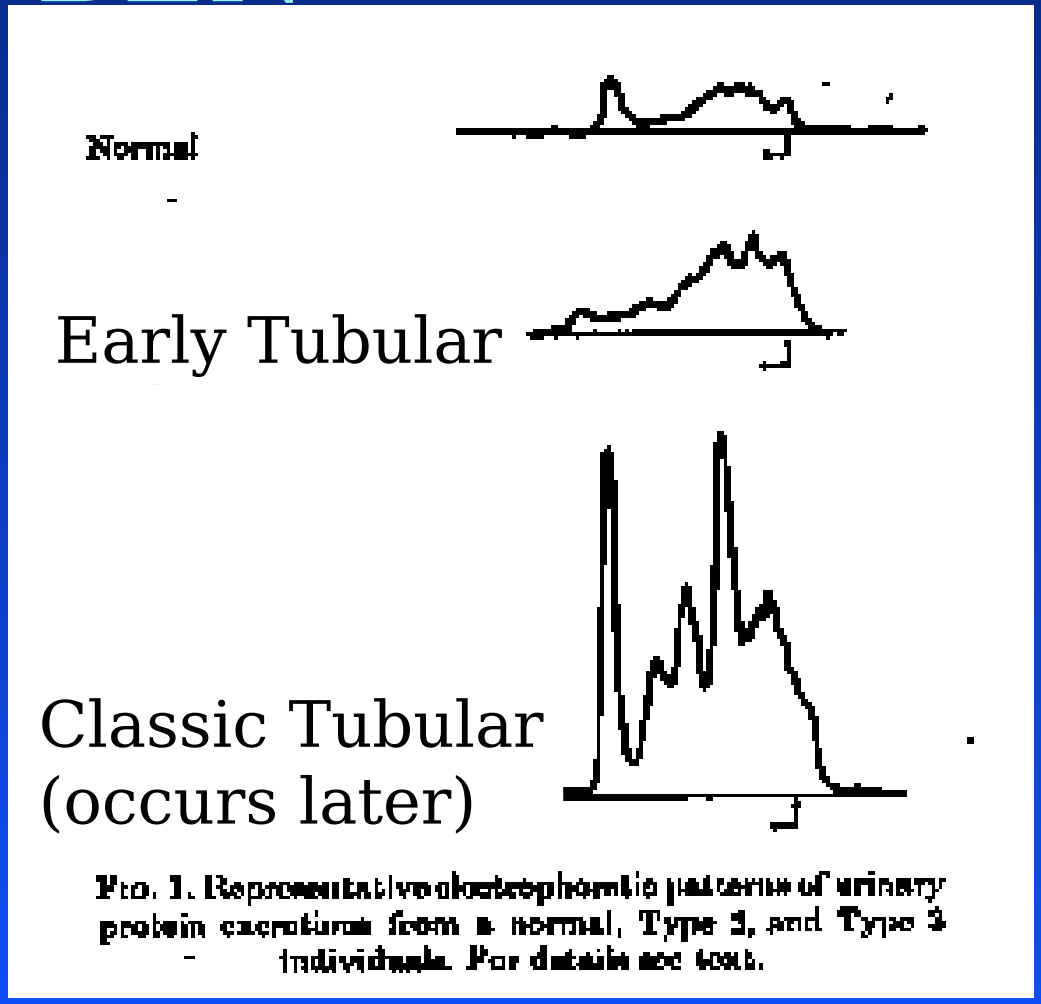


FIG. 1. Representative electrophoretic patterns of urinary protein excretions from a normal, Type 2, and Type 3 individuals. For details see text.

defects in acidifica
ammonia and urate
excretion
(decr PAH Clearan

concentrating defec
elevation in creatini

Hall, Piscator, Vasiljevic & Popovic
Quart. J Med 1972

Pathologic Features of BEN

- Normal or shrunken kidneys
- Early focal tubular atrophy (more in medullary rays) progresses to marked tubular atrophy and fibrosis
- Little cellular infiltrate (mononuclear)
- Few glomerular changes (focal cortical)
- Intimal changes & narrowing of vessels
- Dilation of lymphatics (inadequate lymph drainage ?)

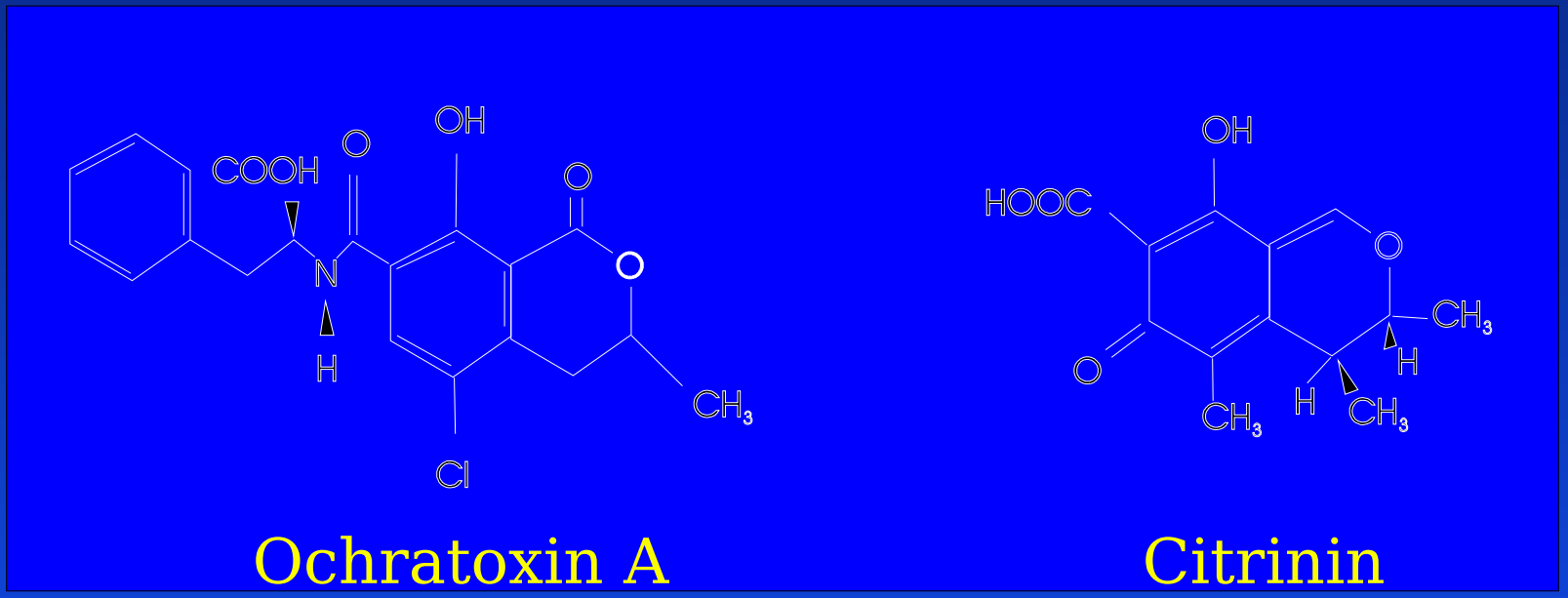
Etiology of BEN
???? still unknown ?????

- Genetic
  - Chromosome 3 in kindreds with dominant inheritance
  - HLA-B18 in Burgaria but not Yugoslavia
  - genetic predisposition
- ? Infection with slow virus ?
- Selenium Defficiency
- Chronic Poisoning
  - unlikely lead or cadmium
  - Mycotoxins
    - Aristolochic Acid
    - Citrinin
    - Ochratoxin A

Ochratoxin A

- produced by *Aspergillus* & *Penicillium*
- widespread contaminant in variety of foods (beer, coffee) & animal feeds
- carcinogenic, teratogenic, mutagenic & immunosupressive
- Nephrotoxic in pigs, rats, chickens (hepatotoxic)
  - Major cause of Nephropathy in Pigs
- Probably Nephrotoxic in Humans
  - Tunisain Nephropathy
  - a case of ARF in Italy (inhalation exposure)
  - brother & sister in France with high blood levels & karyomegaly

Molecular Structure



Ochratoxin A

Citrinin

a structural analog of phenyalanine
inhibits protein synthesis (phen-tRNA aminoacylation)
& induces lipid peroxidation

Renal Effects of OTA in Rats

- Taken up by PAH transporter (blocked by probenicid)
  - plasma binding probably prevents filtration
- Proximal tubule damage (karyomegaly)
  (decr PAH uptake - blocked by Phenylalanine)
- Disturbes pH homeostasis
  - increase in cellular pH & vasa recta pH
- Alkalinizes MDC in culture
- Blocks protien synthesis in Culture
- Stimulates lipid peroxidation (toxicity decreased by SOD)

Possible genetic predispositions for OTA toxicity

- Increased metabolism of debrisoquine (accelerated metabolism through P450)
  - in BEN patients with tumors
  - in animal species more sensitive to OTA-tumors
- Decreased metabolism of OTA

  (proposed in French cases)
- Partial LCAT deficiency

Organisms that make Ochratoxin also produce other nephrotoxins

- Citrinin
- Penicillic Acid
- Rubratoxin A, B
- Viomellein
- Xanthomegnin

The Case for Ochratoxin A (OTA) as the cause of BEN

- Contamination of cerals in endemic village is greater than non-endemic villages
- OTA is found more frequently in blood of BEN patients
- OTA-DNA adducts were found in urinary tract tumors from endemic region

Conclusions

- OTA is certainly nephrotoxic
- Almost certainly can cause human disease
- Potentially additive to other renal toxins
- Should be considered in cases of unknown chronic tubulointerstitial disease
- Popoulations potentially at risk could be screened for increased levels of B2 -microglobulinuria.

Disease does not involve regions historically i